



Centers for Disease Control and Prevention
National Institute for Occupational
Safety and Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, OH 45226-1998

October 23, 2013

J.T.J. Stouten
The Health Council of the Netherlands
PO Box 16052
2500 BB The Hague
The Netherlands

Dear Mr. Stouten:

Thank you for the opportunity to review the draft report on *Ifosfamide* prepared by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety (DECOS), a subcommittee of the Health Council of the Netherlands.

If you have any questions regarding the comments, please contact me at 513-533-8260 (telephone) or by Email at tbl7@cdc.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read "T. J. Lentz".

Thomas J. Lentz, Ph.D., M.P.H.
Branch Chief
Document Development Branch
Education and Information Division

1 Enclosure

**Review comments on Ifosfamide draft document by
David Murray and Samy Rengasamy, NIOSH/NPPTL, 626 Cochrans Mill
Road, Pittsburgh, PA 15236; Kristine Krajnak, NIOSH/HELD, 1095 Willowdale
Road, Morgantown, WV 26506; and Clayton B'Hymer, NIOSH/DART,
4676 Columbia Parkway, Cincinnati, OH 45226**

SECTION & PARAGRAPH	COMMENT
General Comments	Agree with the three classifications. Presumed human reproductive toxicant for effects on fertility and development, insufficient data for effects via lactation.
	Document seems to be accurate and the studies used as supporting data represent what is known regarding the literature.
	The chemical listed is presumed to be a reproductive hazard and should stay that way. There is a developed literature that addresses the occupational hazard of antineoplastic drugs; however, the references are not specific to ifosfamide.
	There are no references that describe the use of personal protective equipment (PPE). Ifosfamide is handled as an aqueous solution that is typically injected intravenously or intraperitoneally or given orally. Some references not included describe detecting residue left on surfaces as a means of accessing exposure for medical workers or cleaning staff thus suggesting that this might be a dermal or respiratory source for exposure.
	There is a surprisingly wide gap between human intravenous dose and animal dose. Could this be due to a daily vs. accumulative dose? Also, it is amazing that significant effects are noticed at the lower animal dosage, but effects in higher doses in humans were minimal, which suggests that the human data may not be adequate.
	<p>Might consider adding references describing occupational exposure to antineoplastic drugs although there is no specific information on ifosfamide. Example:</p> <p><i>Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings</i>, Kopp, B; Schierl, R; Nowak, D International Archives Of Occupational And Environmental Health Volume:86 Issue:1 Pages:47-55 DOI:10.1007/s00420-012-0742-z January 2013</p>

Specific Comments	
Section 2.2	The reference to Longhi et al. should also include the book chapter published by the same authors. It covers the same material, but would be useful if readers could not find the 2003 journal article. The book chapter reference is as follows: Longhi A, Vitali G, Macchiagodena M, Bacci G, <i>Fertility in males and females osterosarcoma patients treated with chemotherapy</i> , in Trends in Bone Cancer Research, Vol. 24, Birch EV editor, 2006, Nova Science Publishing, New York, pp. 247-263.
Page 8, last paragraph	It has been stated that oral administration of ifosfamide produced unacceptable neurotoxicity because oral bioavailability is close to 100%. It looks like intravenous administration will also produce similar toxicity. This point is not described well.
Page 9, Para 1	Total body clearance of ifosfamide is presented as 3.6-8.9 L/h. Please make sure that clearance is presented in the appropriate unit.
Page 13, Para 3	Ehling et al (1998) conducted mutation studies with ifosfamide i.p. administration. After successful matings, females were sacrificed ----- live and dead implantations; results for this description appears to be missing.